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# Synthesis of new chiral bis-imidazolidin-4-ones: comparison between the classic method and green chemistry conditions

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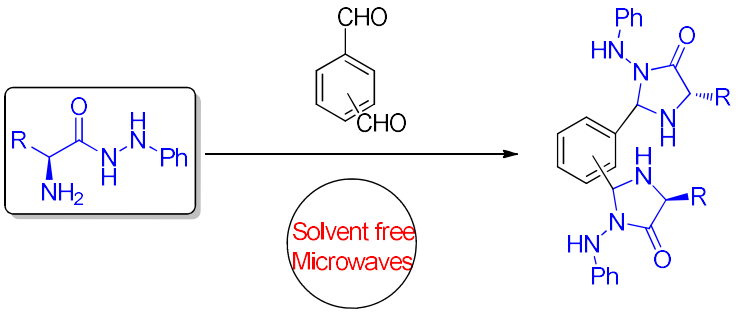
## Abstract

Novel bis-imidazolidin-4-ones were synthesized in moderate to good yields through the cyclocondensation of *o*-, *m*- and *p*-phthalaldehydes with various substituted phenylhydrazides. These nitrogenated cyclic compounds were prepared via green chemistry conditions using microwave irradiation.




R = Me, *i*-Pr, *i*-Bu, Bn, $H_3CS(CH_2)_2$

**Keywords:** Bis-imidazolidin-4-ones, cyclocondensation, phenylhydrazides

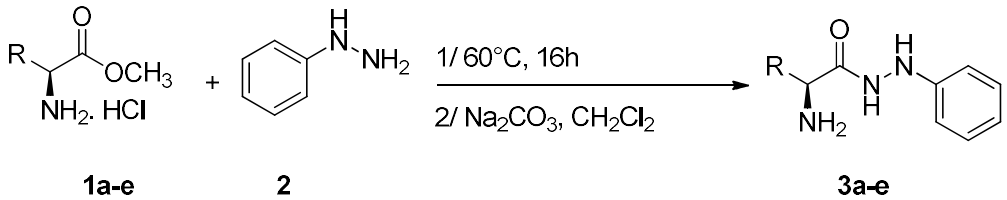
## Introduction

Nitrogen heterocycles are key building blocks for a large number of medicinally-relevant molecules. They constitute an important core fragment in different natural products and pharmaceutical agents.[1] The chemistry of imidazolidinones has recently attracted more attention due to their reactivity and several biological properties. They have been regarded as anthelmintic,[2] analgesic,[3] antibacterial,[4] antifungal,[5] antiviral,[6] antitubercular[7] and anticancer effects,[8] and also as a new chemical class of herbicide.[9] Imidazolidinones can be used as hydrolytically cleavable precursors for the controlled release of fragrant aldehydes and ketones.[9] Considerable efforts have recently been devoted to the development of more efficient approaches for the preparation of imidazolidinone derivatives. They have generally been obtained by condensation of α-aminoamides with carbonyl compounds (aldehyde or ketone).[10] Among these preparations, several studies concerning the synthesis of chiral imidazolidin-4-ones derivatives containing two stereogenic centers using classical conditions have previously been described in papers by Milos.[11-13]

As part of our ongoing efforts directed toward the synthesis of heterocyclic compounds starting from α-amino acids[14-19] and our studies on the reactivity of α-amino acid phenylhydrazides,[20,21] we describe herein a practical and efficient synthetic pathway for the preparation of bis-imidazolidin-4-ones using a green chemistry context (solvent free and without catalyst conditions). To the best of our knowledge, no synthesis of bis-imidazolidin-4-ones have been reported with α-amino acid phenylhydrazide derivatives as starting materials.[1] On the other hand, green or sustainable chemistry has become, over time, a research concept for the development of environmentally and eco-friendly chemistry using products, chemical processes and synthetic pathways that decrease the production of hazardous substances. So, microwave irradiation (MW) is one of the potential green chemistry techniques used during the recent years. The main benefits of performing the reaction under microwave conditions are the higher product yields and the significant rate-enhancements that can be observed. We have used, in this study, a new microwave synthesis system (startSYNTH) that combines sophisticated design and high technology with ease of use and safety.

## Results and Discussion

The starting L-α-amino acid phenylhydrazides **3a-e** were prepared in a manner similar to the well-known procedure described by Verardo *et al*.[22] The commercially available L-α-amino acid ester hydrochlorides **1a-e** reacted with phenylhydrazine (**2**) under mild conditions affording the corresponding phenylhydrazides **3a-e** in good yields (Scheme 1, Table 1).




**1a-e** **2** **3a-e**

**Scheme 1.** Synthesis of substituted α-amino acid phenylhydrazides **3a-e**.

For the investigation of optimal conditions of the coupling reactions, *o*-phthalaldehyde **4a** and L-alanine phenylhydrazide **3a** were employed as reactants (Scheme 2). Two procedures were compared using the same reacting mixtures: the conventional heating with a usual acidic catalyst and in a microwave-assisted approach. First, the use of sulfuric acid or acetic acid as catalysts led to low yields (Table 2, entries 1-3). However, *p*-toluenesulfonic acid brought about a double cyclization up to 94%, mainly due to the use of a higher

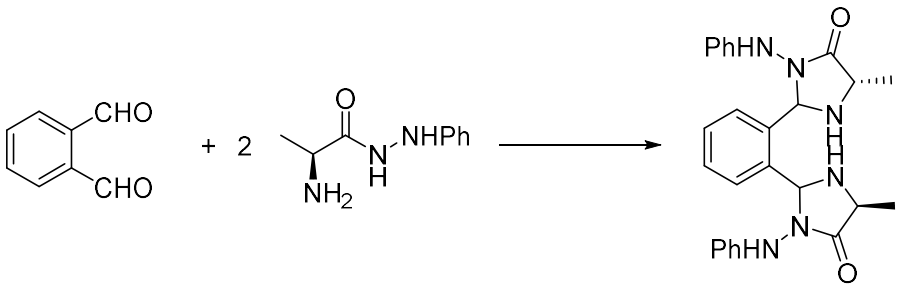
 

temperature, allowing the water vaporization from the appropriate solvent (toluene) and favoring reduced contact of water with the organic materials (entries 4-6). The role of the solvent is tricky to estimate, since it is related to the nature of the catalyst. At first, reactants are not completely soluble in toluene at 70 °C and no reaction was occurred with PTSA or sulfuric acid (results not depicted in table 2); a temperature of 100 °C needed to perform reactions in this solvent. Regardless with the solvent, the reactions conducted with PTSA are much cleaner by TLC compared to $H_2SO_4$ where a big spot was observed for this latter on the baseline, added to numerous new spots. In fact, unidentified side products appeared with sulphuric acid and were insoluble in the medium, likely due to opened forms of the condensation products. To further examine the reactivity of the dialdehyde **4a**, we tried the reaction in the absence of catalyst, but no formation of the desired product was observed (entry 7).

**Table 1.** Synthesis of α-aminoacid phenylhydrazides **3a-e**

| Entry | Product | R | [α] [a] | Yield (%) [b] |
|---|---|---|---|---|
| 1 | **3a** | Me | +34.2 | 85 |
| 2 | **3b** | *i*-Pr | +22.8 | 72 |
| 3 | **3c** | *i*-Bu | +30.8 | 70 |
| 4 | **3d** | $CH_2Ph$ | +39.4 | 85 |
| 5 | **3e** | $(CH_2)_2SMe$ | +29.8 | 79 |

[a] Values were measured in MeOH (c 0.2). [b] Isolated product yield.




**4a** **3a** **5a**

**Scheme 2.** Condensation of *o*-phthalaldehyde **4a** and L-alanine phenylhydrazide **3a**.

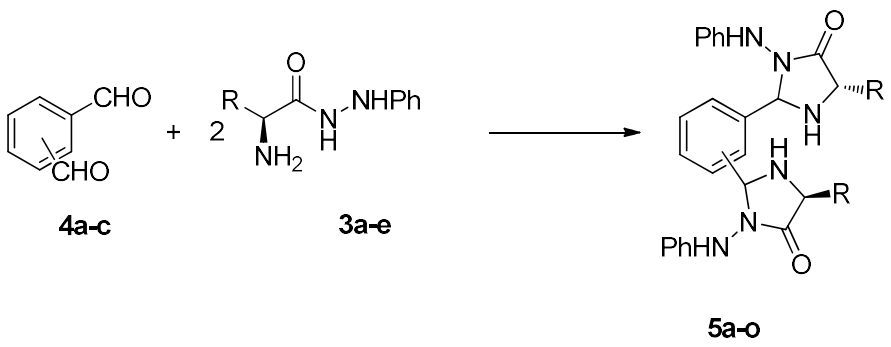
The generalization of the double condensation was next examined with various α-amino acid-derived phenylhydrazides **3a-e** reacting with the 3 isomeric dialdehydes **4a-c** (Scheme 3 and Table 3). The structure of the resulting bis-imidazolidin-4-ones **5a-o** was undoubtedly confirmed based on their analytical and spectral data. The new compounds **5a-o** were isolated as a mixture of two inseparable diastereoisomers (TLC showed always a single spot whatever the eluents used); the duplication of signals on the $^{13}$C-NMR spectrum corroborated the presence of two diastereoisomers. It is worth noting that among the three conceivable diasteroisomers (see supporting information), only two were observed in a 1:1 ratio although the attribution of the stereochemistries of the neo-formed stereocenters was not possible.

**Table 2.** Optimization of reaction conditions for the coupling of o-phthalaldehyde **4a** and L-alanine phenylhydrazide **3a**

| Entry [a] | Catalyst (mol %) | Temp. (°C) | Time (h) | Solvent | Yields (% in **5a**) |
|---|---|---|---|---|---|
| 1 | AcOH (1) | 70 | 24 | EtOH | Trace |
| 2 | $H_2SO_4$ (1) | 70 | 24 | EtOH | <10 |
| 3 | $H_2SO_4$ (1) | 100 | 24 | Toluene | <10 |
| 4 | PTSA (1) | 70 | 10 | EtOH | <10 |
| 5 | PTSA (1) | 85-90 | 24 | Toluene | NR [b] |
| 6 | PTSA (1) | 100 | 24 | Toluene | 94[a] |
| 7 | - | 100 | 24 | Toluene | NR [b] |

[a] Conditions: L-alanine phenylhydrazide (2 mmol), *o*-phthalaldehyde (1 mmol) under argon. [b] No reaction occurred.




**Scheme 3.** Synthesis of the bis-imidazolidin-4-ones **5a-o**.

In conventional heating, the role of the solvent was crucial; thus, for the reaction performed with the o-phthalaldehyde **4a** or the *m*-phthalaldehyde **4b** only a non-polar solvent (toluene) was employed, whereas with the *p*-phthalaldehyde **4c**, a mixture of toluene and ethanol was required due to the lesser solubility of paraphthalaldehyde in toluene compare to the ortho isomer. Moreover, among the phenylhydrazide derivatives **3a-e**, the experiments conducted with L-valine phenylhydrazide **3b** led to low yields (entries 2 , 7 and 12), where the two isopropyl moieties on the resulting products may cause steric hindrance, thermodynamically disfavouring the formation of these corresponding bisimidazolidinones **5b**, **5g**, **5l**. To avoid these limitations, the development of an efficient alternative combining higher yields, shorter reaction times and greener conditions (mild, practical, solvent free) was highly desirable. We had originally hoped that the *o*-, *m*- and *p*-phthalaldehydes could be converted into the corresponding bis-imidazolidin-4-ones with a non classical heating. Moving to a methodology using microwave irradiation at 100 °C in both solvent- and catalyst free conditions, reactions were completed in only 6 minutes affording the expected bis-imidazolidin-4-ones **5a-o** in higher yields. We were pleased to find that these conditions efficiently proceeded to afford the desired products without any trace of the starting dialdehydes or the monocondensation product. The heterocycles **5a-o** are very silica gel sensitive compounds and numerous attempts failed to isolate them even though basifying the silica gel with triethylamine, in all cases the corresponding starting dialdehydes **4a-c** were

recovered. We succeeded in isolating a mixture of the two diastereoisomers by crystallization using dichloromethane and diethyl ether (7:3). The workup was considerably simpler since a simple crystallization from the crude rapidly gave the targeted heterocycles.

**Table 3.** Coupling of the phenylhydrazides **3a-e** with the dialdehydes **4a-c**

| Entry | Substrate | Reactant | Product | Yields Δ (%) [a] | Yields MW (%)[b] |
|---|---|---|---|---|---|
| 1 | **4a** | **3a** | **5a** | 94 | 96 |
| 2 | **4a** | **3b** | **5b** | 34 | 55 |
| 3 | **4a** | **3c** | **5c** | 79 | 81 |
| 4 | **4a** | **3d** | **5d** | 65 | 66 |
| 5 | **4a** | **3e** | **5e** | 60 | 72 |
| 6 | **4b** | **3a** | **5f** | 82 | 93 |
| 7 | **4b** | **3b** | **5g** | 32 | 46 |
| 8 | **4b** | **3c** | **5h** | 67 | 88 |
| 9 | **4b** | **3d** | **5i** | 69 | 71 |
| 10 | **4b** | **3e** | **5j** | 71 | 80 |
| 11 | **4c** | **3a** | **5k** | 59 | 45 |
| 12 | **4c** | **3b** | **5l** | 11 | 32 |
| 13 | **4c** | **3c** | **5m** | 71 | 84 |
| 14 | **4c** | **3d** | **5n** | 78 | 89 |
| 15 | **4c** | **3e** | **5o** | 67 | 80 |

[a] Conventional heating (oil bath) in toluene (10 mL) for *o*-phthalaldehyde **4a** or else in toluene/EtOH (10 mL) for *p*-phthalaldehyde **4c**. [b] Conditions of activation: microwave irradiation (startSYNTH), 100 °C, 6 min.

The conditions under which the reactions summarised in Table 2 were performed are as follows:
*Entries 1-5*: *o*-phthalaldehyde **4a** (1.4 mmol), α-amino acid phenylhydrazide **3** (2.8 mmol), PTSA (10 % mol), 100 °C, 24 h under argon.
*Entries 6-10*: *m*-phthalaldehyde **4b** (1.4 mmol), α-amino acid phenylhydrazide (2.8 mmol), PTSA (10 % mol), 100 °C, 24 h under argon.
*Entries 11-15*: *p*-phthalaldehyde **4c** (1.4 mmol), α-amino acid phenylhydrazide **3a-e** (2.8 mmol), PTSA (10 % mol), 100 °C, 24 h under argon.

## Conclusions

In conclusion, we have developed a straightforward and efficient method for the synthesis of new bis-imidazolidin-4-ones in moderate to good yields under catalytic conditions. The improvement in processing was pursued up to an approach using the solvent free microwave irradiation in soft conditions (no metal and no catalyst) leading to original nitrogenated compounds with respect to the green chemistry conditions and an easy-to-operate procedure, including the purification by crystallization.

## Experimental Section

**General.** All reagents and chemicals were purchased from Sigma-Aldrich chemical company and Acros Organics. Solvents used in reactions were dried and distilled before use. Toluene was distilled over sodium metal, and EtOH was distilled over $Mg/I_2$. Nuclear magnetic resonance (NMR) was recorded on Bruker AC-300 spectrometers ($^1H$ at 300 MHz and $^{13}C$ at 75 MHz) in deuterochloroform ($CDCl_3$) as solvent. NMR chemical shifts were calibrated on the solvent residual signal at 7.26 ppm for $^1H$ and at 77.16 ppm for $^{13}C$. In most cases, the $^{13}C$ NMR spectra showed a duplication of the chemical shifts signals (presence of two diastereoisomers) and are described herein in this sense, therefore with the twice carbon number vis-à-vis the formula weight. Infrared spectra (IR) were obtained using a Perkin Elmer spectrometer in the range 4000-400 $cm^{-1}$. Electrospray ionisation (ESI) mass spectroscopy data of compounds **5a**, **5c**, **5d**, **5e**, **5k**, **5m**, **5n**, **5o** were recorded on an UPLC Waters device (in positive mode); for the voltages of the mass spectroscopies, the following abbreviations are used: C Capillary (kV), SC Sampling Cone, EC Extraction Cone. Calibration was performed with sodium formate (range from 100 to 1000 $g.mol^{-1}$) and the lockspray (lockmass on the leucine encephaline 556.2771 $g.mol^{-1}$) was used without collision energy; the relative intensity of peaks is given in brackets. Electrospray ionisation (ESI) mass spectroscopy data of compounds **5b**, **5f**, **5h**, **5i** and **5j** were recorded on a Q exactive hybrid quadrupole-orbitrap mass spectrometer coupled to a U3000 LC device; the spray voltage was 3000 V. The positive ion calibration was performed with a commercially available mixture of caffeine, MRFA, Ultramark1621 and n-butylamine in a acetonitrile /methanol/acetic acid solution. Characterisation of the compounds **5a-o** described herein is for thermal experiment; yields for conventional heating and microwave activation are given in Table 3.

**General procedure for the synthesis of bis-imidazolidin-4-ones 5**

**Catalytic conditions.** To a stirred solution of the α-amino acid phenylhydrazide **3a-e** (2.8 mmol, 2 eq) and the *o*-phthalaldehyde **4a**, *m*-phthalaldehyde **4b** or the *p*-phthalaldehyde **4c** (187.7 mg, 1.4 mmol, 1 eq) in dry toluene (10 mL), was added PTSA (24.10 mg, 0.14 mmol, 10 % mol), and the mixture was heated for 24 h under an inert atmosphere. After evaporating the solvent under reduced pressure, the residue was dissolved in $CH_2Cl_2$ (50 mL) and then the mixture was vigorously stirred with $Na_2CO_3$ (0.24 g, 8.38 mmol) and $H_2O$ (1.17 mL, 65 mmol) for 30 min. The solution was dried over anhydrous $Na_2SO_4$ and filtered. The solvent was evaporated to obtain a pale-yellow solid, which was purified by precipitation from $CH_2Cl_2/Et_2O$ 7:3 (10 mL) then filtered to afford pure **5a-o**. These products could not be purified by absorption chromatography since they extensively decomposed upon contact on silica gel or alumina.

**Solvent free microwave irradiation.** A mixture of α-amino acid phenylhydrazide **3a-e** (2.8 mmol, 2 eq) and the *o*-phthalaldehyde **4a** the *m*-phthalaldehyde **4b** or the *p*-phthalaldehyde **4c** (187.7 mg, 1.4 mmol, 1 eq) was submitted to programmed microwave synthesis reactor (START SYNTH) at 100 °C for 6 min. The crude product was purified by precipitation in a mixture of $CH_2Cl_2/Et_2O$ 7:3 (10 mL) in a refrigerator at 3 °C, then filtered to afford pure **5a-o**.

**(1,2-Phenylene)-2,2′-bis-[5-methyl-3-(phenylamino)imidazolidin-4-one]** (**5a**). White solid, mp 115-117 °C. $R_f$ 0.17 (EtOAc : c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3251, 2973, 1697, 1597, 1298. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ 1.47 (6H, d, $^3J_{HH}$ 6.6 Hz), 2.15 (2H, s, NH), 3.81 (2H, q, $^3J_{HH}$ 6.6 Hz), 5.57 and 5.59 (2 x 1H, 2s, CH), 5.76 and 5.78 (2 x 1H, 2s, NHPh), 6.55-6.66 (4H, m, CH aromatic), 6.85-6.92 (2H, m, CH aromatic), 7.21-7.24 (4H, m, CH aromatic), 7.37-7.42 (4H, m, CH aromatic). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ 18.22 (2 x $CH_3$), 18.49 (2 x $CH_3$), 52.61 (2 x CH), 53.39 (2 x CH), 74.12 (2 x CH), 74.70 (2 x CH), 113.62 (4 x CH aromatic), 113.92 (4 x CH aromatic),

121.52 (2 x CH aromatic), 121.61 (2 x CH aromatic), 126.18 (2 x CH aromatic), 128.22 (2 x CH aromatic), 128.55 (2 x CH aromatic), 129.26 (4 x CH aromatic), 129.37 (4 x CH aromatic), 129.73 (2 x C aromatic), 138.83 (2 x C aromatic), 139.46 (2 x C aromatic), 145.22 (2 x NHC aromatic), 145.25 (2 x NHC aromatic), 174.45 (2 x C=O), 174.71 (2 x C=O). ESI(+)-MS $CH_3CN$ [C = 0.5, SC = 30, EC = 3] *m/z* (rel. int.): 457 (100, M + $H^+$), 386 (20, M-CONHCHMe + $H^+$), 315 (50), 295 (15); HRMS $ES^+$ for $C_{26}H_{29}N_6O_2$ $[M+H]^+$ Calc. 457.2352, found: 457.2349.

**2,2′-(1,2-Phenylene)bis-[5-isopropyl-3-(phenylamino)imidazolidin-4-one]** (**5b**). White solid, mp 112-114 °C. $R_f$ 0.22 (EtOAc/c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3311, 1600, 1554, 1294. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ 0.89 (12H, d, $^3J_{HH}$ 7,6 Hz), 2.02 (2H, s, NH), 2.14-2.17 (2H, m, $CH(CH_3)_2$), 3.56 (2H, d, $^3J_{HH}$ 6.2 Hz), 6.33 and 6.36 (2 x 1H, 2s, CH), 6.65 and 6.67 (2 x 1H, 2s, NHPh), 6.91-6.96 (4H, m, CH aromatic), 7.11 (2H aromatic, t, $^3J_{HH}$ 7.4 Hz), 7.16 (4H aromatic, d, $^3J_{HH}$ 8.09 Hz), 7.18 (2H aromatic, d, $^3J_{HH}$ 8.09 Hz), 7.35-7.38 (2H, m, CH aromatic). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ 20.22 (2 x $2CH_3$), 32.13 ($CH(CH_3)_2$), 32.17 ($CH(CH_3)_2$), 74.09 (CH), 74.11 (CH), 80.70 (2 x CHC=O), 80.73 (2 x CHC=O), 115.11 (2 x CH aromatic), 117.23 (2 x CH aromatic), 126.55 (2 x CH aromatic), 129.45 (2 x CH aromatic), 131.09 (2 x CH aromatic), 142.16 (2 x C aromatic), 155.01 (2 x NHC aromatic), 174.11 (2 x C=O), 174.14 (2 x C=O). HRMS $ES^+$ ($CH_3CN$) for $C_{30}H_{37}N_6O_2$ *m/z*: $[M+H]^+$ Calc. 513.2911, found: 513.2914.

**2,2′-(1,2-Phenylene)bis-[5-isobutyl-3-(phenylamino)imidazolidin-4-one]** (**5c**). White solid, mp 118-120 °C. $R_f$ 0.30 (EtOAc/c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3280, 2955, 1700, 1601, 1496, 1246. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ 0.98 (6H, d, $^3J_{HH}$ 6.3 Hz), 1.04 (6H, d, $^3J_{HH}$ 6.6 Hz), 1.47-1.51 (2H, m, $CH(CH_3)_2$), 1.75-1.92 (4H, m, $CH_2$), 2.19 (2H, s, NH), 5.59 (2H, t, $^3J_{HH}$ 6.6 Hz), 6.53 and 6.56 (2 x 1H, 2s, CH), 6.59 and 6.62 (2 x 1H, 2s, NHPh), 6.63-6.69 (4H, m, CH aromatic), 6.90 (2H, t, $^3J_{HH}$ 8.1 Hz), 7.12-7.24 (4H, m, CH aromatic), 7.37-7.46 (4H, m, CH aromatic). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ 21.45 (2 x $CH_3$), 23.44 (2 x $CH_3$), 29.71 (2 x CH), 41.81 ($CH_2$), 41.90 ($CH_2$), 55.27 (CH), 55.35 (CH), 74.52 (2 x CH), 74.80 (2 x CH), 113.63 (2 x CH aromatic), 121.59 (2 x CH aromatic), 126.35 (2 x CH aromatic), 127.14 (2 x CH aromatic), 129.53 (2 x CH aromatic), 138.56 (2 x C aromatic), 145.22 (2 x NHC aromatic), 174.77 (2 x C=O), 174.84 (2 x C=O). ESI(+)-MS $CH_3CN$ [C = 0.5, SC = 30, EC = 3] *m/z* (rel. int.): 541 (50, M + $H^+$), 428 (35, M-COCHiBuNH + $H^+$), 315 (100), 149 (55). HRMS $ES^+$ for $C_{32}H_{41}N_6O_2$ *m/z*: $[M+H]^+$ Calc. 541.3291, found: 541.3296.

**2,2′-(1,2-Phenylene)bis-[5-benzyl-3-(phenylamino)imidazolidin-4-one]** (**5d**). White solid, mp 124-126 °C. $R_f$ 0.29 (EtOAc/c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3255, 1623, 1354, 1237. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ 1.95 (2H, s, NH), 3.22 (2H, dd, $^3J_{HH}$ 12.3, $^3J_{HH}$ 6.00 Hz), 3.41 (2H, dd, $^3J_{HH}$ 12.3, $^3J_{HH}$ 6.00 Hz), 4.00 (2H, t, $^3J_{HH}$ 6.00 Hz), 6.27 and 6.30 (2 x 1H, 2s, CH), 6.48 and 6.50 (2 x 1H, 2s, NHPh), 6.79-6.97 (4H, m, CH aromatic), 7.05-7.20 (4H, m, CH aromatic), 7.23-7.29 (8H, m, 4CH aromatic), 7.37-7.39 (8H, m, 4CH aromatic). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ 37.66 ($CH_2$), 37.68 ($CH_2$), 74.22 (2 x CHC=O), 74.25 (2 x CHC=O), 77.44 (2 x CH), 77.47 (2 x CH), 113.51 (2 x CH aromatic), 113.57 (2 x CH aromatic), 114.04 (2 x CH aromatic), 121.51 (2 x CH aromatic), 125.42 (2 x CH aromatic), 127.17 (2 x CH aromatic), 128.82 (CH aromatic), 128.88 (CH aromatic), 129.23 (2 x CH aromatic), 129.86 (2 x CH aromatic), 130.09 (2 x CH aromatic), 136.28 (2 x C aromatic), 139.83 (2 x C aromatic), 144.95 (2 x NHC aromatic), 172,69 (2 x C=O). ESI(+)-MS $CH_3CN$ [C = 0.5, SC = 30, EC = 3] *m/z* (rel. int.): 609 (100, M + $H^+$), 462 (40, M-CONHCHBn + $H^+$), 315 (40), 120 (60). HRMS $ES^+$ for $C_{38}H_{37}N_6O_2$ *m/z*: $[M+H]^+$ Calc. 609.2978, found: 609.2976.

**2,2′-(1,2-Phenylene)bis-[5-(2-methylthioethyl)-3-(phenylamino)imidazolidin-4-one]** (**5e**). White solid, mp 123-125 °C. $R_f$ 0.45 (EtOAc/c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3275, 1690, 1367, 1278. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ 1.91-2.15 (2H, m, CH), 2.16 (6H, s, $SCH_3$), 2.19-2.38 (2H, m, CH), 2.62 (2H, s, NH), 2.75-2.79 (4H, m, $CH_2$), 3.96-4.01 (2H, m, CHC=O), 5.56 and 5.60 (2 x 1H, 2s, CH), 5.63 and 5.83 (2 x 1H, 2s, NHPh), 6.57 (2H, d, $^3J_{HH}$ 8.1 Hz), 6.65 (2H, d, $^3J_{HH}$ 7.8 Hz), 6.86-6.94 (2H, m, CH aromatic), 7.13-7.23 (4H, m, CH aromatic), 7.33-7.51 (4H, m, CH aromatic). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ 15.31 ($CH_2$), 15.37, ($CH_2$), 30.35 ($SCH_3$), 31.48 ($CH_2$), 31.67 ($CH_2$), 55.65 (2 x CH), 56.13 (2 x CH), 74.38 (2 x CH), 74.82 (2 x CH), 113.69 (2 x CH aromatic), 113.84 (2 x CH

aromatic), 121.62 (2 x CH aromatic), 122.28 (CH aromatic), 126.21 (CH aromatic), 129.27 (2 x CH aromatic), 139.12 (C aromatic), 145.25 (2 x NHC aromatic), 173.36 (2 x C=O), 173.73 (2 x C=O). ESI(+)-MS $CH_3CN$ [C = 0.5, SC = 30, EC = 3] *m/z* (rel. int.): 577 (100, M + $H^+$), 446 (5, M-CONHCH$(CH_2)_2$SMe + $H^+$), 355 (10). HRMS $ES^+$ for $C_{30}H_{37}N_6O_2S_2$ *m/z*: $[M+H]^+$ Calc. 577.2419, found: 577.2416.

**2,2′-(1,3-Phenylene)bis-[5-methyl-3-(phenylamino)imidazolidin-4-one]** (**5f**). White solid, mp 116-118 °C. $R_f$ 0.18 (EtOAc/c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3253, 3024, 1707, 1694, 1600, 1495. $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ 1.52 and 1.54 (6H, 2d, $^3J_{HH}$ 6.6 Hz), 1.80 (2H, broad s, NH), 3.81 (2H, q, $^3J_{HH}$ 6.6 Hz), 5.55 and 5.58 (2 x 1H, 2s, CH), 5.76 and 5.78 (2 x 1H, 2s, NHPh), 6.55-6.66 (4H, m, CH aromatic), 7.11-7.15 (2H, m, CH aromatic), 7.21-7.24 (4H, m, CH aromatic), 7.37-7.42 (4H, m, CH aromatic). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ 18.29 (2 x $CH_3$), 18.50 (2 x $CH_3$), 52.67 (2 x CH), 53.35 (2 x CH), 73.97 (2 x CH), 74.40 (2 x CH), 113.74 (4 x CH aromatic), 113.98 (4 x CH aromatic), 121.61 (4 x CH aromatic), 121.75 (4 x CH aromatic), 127.57 (2 x CH aromatic), 128.41 (2 x CH aromatic), 129.25 (4 x CH aromatic), 129.38 (4 x CH aromatic), 139.05 (2 x CH aromatic), 140.09 (2 x C aromatic), 145.08 (2 x NHC aromatic), 145.24 (2 x NHC aromatic), 174.48 (2 x C=O), 174.55 (2 x C=O). ESI(+)-MS $CH_3CN$ *m/z* (rel. int.): 530 (15), 495 (10, M + $K^+$), 479 (60, M + $Na^+$), 457 (100, M + $H^+$). HRMS $ES^+$ for $C_{26}H_{29}N_6O_2$ *m/z*: $[M+H]^+$ Calc. 457.2347, found: 457.2342.

**2,2′-(1,3-Phenylene)bis-[5-isopropyl-3-(phenylamino)imidazolidin-4-one]** (**5g**). White solid, mp 111-113 °C. $R_f$ 0.21 (EtOAc/c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3300, 1620, 1543, 1290. $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ 0.91 (12H, d, $^3J_{HH}$ 7.4 Hz), 2.00 (2H, s, NH), 2.16-2.18 (2H, m, CH$(CH_3)_2$), 3.74 (2H, d, $^3J_{HH}$ 6.2 Hz), 6.31 and 6.33 (2 x 1H, 2s, CH), 6.55 and 6.57 (2 x 1H, 2s, NHPh), 6.87-6.90 (4H, m, CH aromatic), 7.09 (2H, t, $^3J_{HH}$ 7.9 Hz), 7.14 (4H, d, $^3J_{HH}$ 8.1 Hz), 7.18 (2H, d, $^3J_{HH}$ 8.1 Hz), 7.32-7.36 (2H, m, CH aromatic). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ 20.44 ($(CH_3)_2$), 31.23 (CH), 31.25 (CH), 73.19 (CH), 73.21 (CH), 83.73 (2 x CH), 83.75 (2 x CH), 115.13 (2 x CH aromatic), 116.25 (2 x CH aromatic), 126.45 (2 x CH aromatic), 128.62 (2 x CH aromatic), 130.15 (2 x CH aromatic), 131.11 (2 x CH aromatic), 142.54 (2 x C aromatic), 156.41 (2 x NHC aromatic), 174.41 (2 x C=O), 174.43 (2 x C=O).

**2,2′-(1,3-Phenylene)bis-[5-isobutyl-3-(phenylamino)imidazolidin-4-one]** (**5h**). White solid, mp 119-121 °C. $R_f$ 0.28 (EtOAc/c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3032, 2954, 2628, 1579, 1512, 1405. $^1$H-NMR (300 MHz, $CDCl_3$): δ = 1.00 (6H, d, $^3J_{HH}$ 5.7 Hz), 1.04 (6H, d, $^3J_{HH}$ 6.3 Hz), 1.56-1.62 (2H, m, CH$(CH_3)_2$), 1.88-1.90 (4H, m, $CH_2$), 2.18 (2H, s, NH), 3.85 (2H, dd, $^3J_{HH}$ 14.4, $^3J_{HH}$ 8.4 Hz), 5.61 and 5.63 (2 x 1H, 2s, CH), 5.69 and 5.71 (2 x 1H, 2s, NHPh), 6.61-6.70 (4H, m, CH aromatic), 6.88-6.95 (2H, m, CH aromatic), 7.16-7.28 (4H, m, CH aromatic), 7.29-7.45 (4H, m, CH aromatic). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ 21.45 (4 x $CH_3$), 21.47 (4 x $CH_3$), 25.08 (2 x CH), 42.03 (2 x $CH_2$), 42.07 (2 x $CH_2$), 55.29 (2 x CH), 55.91 (2 x CH), 74.21 (2 x CH), 74.58 (2 x CH), 113.75 (4 x CH aromatic), 114.00 (4 x CH aromatic), 121.57 (4 x CH aromatic), 121.69 (4 x CH aromatic), 127.62 (2 x CH aromatic), 128.49 (2 x CH aromatic), 129.23 (4 x CH aromatic), 129.36 (4 x CH aromatic), 140.22 (2 x C aromatic), 145.14 (2 x NHC aromatic), 145.26 (2 x NHC aromatic), 174.44 (2 x C=O), 174.68 (2 x C=O). ESI(+)-MS $CH_3CN$ *m/z* (rel. int.): 579 (15, M + $K^+$), 563 (100, M + $Na^+$), 541 (75, M + $H^+$), 464 (15, M-Ph + $H^+$), 453 (55), 413 (10), 391 (15). HRMS $ES^+$ for $C_{30}H_{41}N_6O_2$ *m/z*: $[M+H]^+$ Calc. 541.3286, found: 541.3282.

**2,2′-(1,3-Phenylene)bis-[5-benzyl-3-(phenylamino)imidazolidin-4-one]** (**5i**). White solid, mp 127-129 °C. $R_f$ 0.29 (EtOAc/c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3294, 2920, 1699, 1601, 1495, 1453, 1090. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta_H$ 1.14 (2H, s, NH), 3.10-3.30 (4H, m, $CH_2$), 3.99-4.09 (2H, m, CH), 5.20 and 5.27 (2 x 1H, 2s, CH), 5.43 and 5.48 (2 x 1H, 2s, NHPh), 6.18-6.27 (2H, m, CH aromatic), 6.41-6.44 (2H, m, CH aromatic), 6.64-6.68 (2H, m, CH aromatic), 6.78-6.80 (4H, m, CH aromatic); 7.00-7.07 (6H, m, CH aromatic), 7.19-7.29 (8H, m, CH aromatic). $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta_C$ 37.98 ($CH_2$), 38.01 ($CH_2$), 55.23 (2 x CH), 55.25 (2 x CH), 77.01 (2 x CH), 77.03 (2 x CH), 113.11 (2 x CH aromatic), 115.02 (2 x CH aromatic), 122.12 (2 x CH aromatic), 125.55 (2 x CH aromatic), 127.56 (2 x CH aromatic), 128.11 (2 x CH aromatic), 128.61 (2 x CH aromatic), 129.21 (2 x CH aromatic), 129.45

(CH aromatic), 131.13 (CH aromatic), 137.33 (2 x C aromatic), 139.23 (2 x C aromatic), 145.54 (2 x NHC aromatic), 145.66 (2 x NHC aromatic), 171.34 (2 x C=O). ESI(+)-MS $CH_3CN$ *m/z* (rel. int.): 647 (20, M + $K^+$), 631 (95, M + $Na^+$), 609 (100, M + $H^+$), 566 (15), 453 (30), 343 (10, M-imidazolidinone + $H^+$), 294 (25), 272 (35). HRMS $ES^+$ for $C_{38}H_{37}N_6O_2$ *m/z*: $[M+H]^+$ Calc. 609.2973, found: 609.2966.

**2,2′-(1,3-Phenylene)bis-[5-(2-methylthioethyl)-3-(phenylamino)imidazolidin-4-one]** (**5j**). White solid, mp 124-126 °C. $R_f$ 0.46 (EtOAc/c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3278, 2913, 1695, 1601, 1495, 1445, 1092. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ 1.96-2.06 (2H, m, CH), 2.14 (6H, s, $CH_3$), 2.31-2.62 (2H, m, CH), 2.74-2.96 (4H, m, $CH_2$), 4.00-4.04 (2H, m, CH), 5.52 and 5.62 (2 x 1H, 2s, CH), 5.64 and 5.69 (2 x 1H, 2s, NHPh), 6.54-6.61 (4H, m, CH aromatic), 6.65-6.71 (2H, m, CH aromatic), 7.15-7.20 (4H, m, CH aromatic), 7.33-7.37 (4H, m, CH aromatic), 7.42-7.47 (2H, m, CH aromatic). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ 15.27 (4 x $CH_2$), 15.36 (4 x $CH_2$), 30.34 (4 x $SCH_3$), 31.51 (2 x $CH_2$), 31.59 (2 x $CH_2$), 74.40 (2 x CH), 74.44 (2 x CH), 77.43 (2 x CH), 77.50 (2 x CH), 113.72 (4 x CH aromatic), 113.94 (4 x CH aromatic), 121.66 (2 x CH aromatic), 122.04 (2 x CH aromatic), 125.23 (4 x CH aromatic), 128.78 (4 x CH aromatic), 129.38 (4 x CH aromatic), 134.13 (4 x C aromatic), 145.55 (4 x NHC aromatic), 173.31 (2 x C=O), 173.35 (2 x C=O). ESI(+)-MS $CH_3CN$ *m/z* (rel. int.): 615 (10, M + $K^+$), 599 (70, M + $Na^+$), 577 (100, M + $H^+$), 453 (10). HRMS $ES^+$ for $C_{30}H_{37}N_6O_2S_2$ *m/z*: $[M+H]^+$ Calc. 577.2414, found: 577.2408.

**2,2′-(1,4-Phenylene)bis-[5-methyl-3-(phenylamino)imidazolidin-4-one]** (**5k**). White solid, mp 117-119 °C. $R_f$ 0.17 (EtOAc/c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3254, 3022, 1708, 1600, 1495, 1392. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ 1.44 (6H, d, $^3J_{HH}$ 6.9 Hz), 2.00 (2H, s, NH), 3.74 (2H, q, $^3J_{HH}$ 6.9 Hz), 6.00 and 6.02 (2 x 1H, 2s, CH), 6.70 and 6.72 (2 x 1H, 2s, NHPh), 6.78 (4H, dd, $^3J_{HH}$ 7.2, $^3J_{HH}$ 6.9 Hz), 6.85-6.92 (2H, m, CH aromatic), 7.12-7.22 (4H, m, CH aromatic), 7.34-7.48 (4H, m, CH aromatic). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ 23.70 (2 x $CH_3$), 23.71 (2 x $CH_3$), 51.81 (2 x CH), 51.83 (2 x CH), 75.19 (2 x CH), 75.21 (2 x CH), 113.22 (4 x CH aromatic), 113.24 (4 x CH aromatic), 122.82 (4 x CH aromatic), 125.39 (4 x CH aromatic), 125.41 (4 x CH aromatic), 129.26 (4 x CH aromatic), 129.27 (4 x CH aromatic), 137.83 (2 x C aromatic), 137.86 (2 x C aromatic), 151.00 (2 x NHC aromatic), 151.03 (2 x NHC aromatic), 173.41 (2 x C=O), 173.43 (2 x C=O). ESI(+)-MS $CH_3CN$ [C = 0.5, SC = 30, EC = 3] *m/z* (rel. int.): 935 (5, 2M + $Na^+$), 457 (50, M + $H^+$), 386 (40, M-COCHMeNH + $H^+$), 315 (100), 242 (10). HRMS $ES^+$ for $C_{26}H_{29}N_6O_2$ *m/z*: $[M+H]^+$ Calc. 457.2352, found: 457.2346.

**2,2′-(1,4-Phenylene)bis-[5-isopropyl-3-(phenylamino)imidazolidin-4-one]** (**5l**). Yellow liquid, mp 113-115 °C. $R_f$ 0.22 (EtOAc/c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3330, 1601, 1555, 1300. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ 1.00 (12H, d, $^3J_{HH}$ 6.2 Hz), 1.92 (2H, s, NH), 2.28-2.31 (2H, m, CH), 3.65 (2H, d, $^3J_{HH}$ 7.4 Hz), 6.00 and 6.02 (2 x 1H, 2s, CH), 6.62 and 6.64 (2 x 1H, 2s, NHPh), 7.24-7.26 (4H, m, CH aromatic), 7.38-7.41 (10H, m, CH aromatic). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ 20.15 (2 x $(CH_3)_2$), 20.19 (2 x $(CH_3)_2$), 33.00 (CH), 33.04 (CH), 74.60 (CH), 74.66 (CH), 75.20 (2 x CH), 75.24 (2 x CH), 113.30 (2 x CH aromatic), 122.02 (CH aromatic), 126.00 (CH aromatic), 127.00 (2 x CH aromatic), 130.10 (2 x C aromatic), 151.30 (2 x NHC aromatic), 173.30 (2 x C=O), 173.32 (2 x C=O).

**2,2′-(1,4-Phenylene)bis-[5-isobutyl-3-(phenylamino)imidazolidin-4-one]** (**5m**). White solid, mp 120-122°C. $R_f$ 0.33 (EtOAc/c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3263, 2957, 1703, 1602, 1497, 1082. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ 1.01 (6H, d, $^3J_{HH}$ 6.4 Hz), 1.05 (6H, d, $^3J_{HH}$ 6.7 Hz), 1.55-1.59 (2H, m, CH), 1.88-1.90 (4H, m, $CH_2$), 3.82-3.85 (2H, m, CH), 5.59 (2H, s, CH), 5.61 (2H, s, NH), 6.87-6.92 (4H, m, CH aromatic), 7.05 (4H, d, $^3J_{HH}$ 8.7 Hz), 7.08-7.11 (4H, m, CH aromatic), 7.33-7.37 (4H, m, CH aromatic). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ 21.51 ($CH_3$), 23.36 ($CH_3$), 25.09 (2 x CH), 42.04 ($CH_2$), 42.10 ($CH_2$), 55.29 (CH), 55.92 (CH), 74.26 (CH), 74.65 (CH), 113.81 (2 x CH aromatic), 121.59 (2 x CH aromatic), 121.70 (2 x CH aromatic), 127.59 (2 x CH aromatic), 127.68 (2 x CH aromatic), 129.20 (2 x CH aromatic), 129.33 (2 x CH aromatic), 140.25 (2 x C aromatic), 145.20 (NHC aromatic), 145.32 (NHC aromatic), 174.39 (2 x C=O), 174.64 (2 x C=O). ESI(+)-MS $CH_3CN$ [C = 2, SC = 20, EC = 2] *m/z* (rel. int.): 631 (15), 563 (100, M + $Na^+$), 541 (90, M + $H^+$), 428 (10, M-COCHiBuNH + $H^+$), 301 (15), 242 (25). HRMS $ES^+$ for $C_{32}H_{41}N_6O_2$ *m/z*: $[M+H]^+$ Calc. 541.3291, found: 541.3293.

**2,2′-(1,4-Phenylene)bis-[5-benzyl-3-(phenylamino)imidazolidin-4-one]** (**5n**). White solid, mp 129-131°C. $R_f$ 0.28 (EtOAc/c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3277, 3031, 1699, 1590, 1398. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta_H$ 1.28 (2H, s, NH), 3.41 (2H, dd, $^3J_{HH}$ 12.3, $^3J_{HH}$ 6.0 Hz), 3.55 (2H, dd, $^3J_{HH}$ 12.3, $^3J_{HH}$ 6.0 Hz), 4.02 (2H, t, $^3J_{HH}$ 6.0 Hz), 4.09 (2H, t, $^3J_{HH}$ 6.0 Hz), 6.27 and 6.30 (2 x 1H, 2s, CH), 6.48 and 6.50 (2 x 1H, 2s, NHPh), 6.79-6.97 (8H, m, CH aromatic), 7.05-7.20 (3H, m, CH aromatic), 7.23-7.29 (8H, m, CH aromatic), 7.37-7.39 (3H, m, CH aromatic). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ 36.84 ($CH_2$), 57.74 (CH), 58.40 (CH), 73.88 (2 x CH), 74.83 (2 x CH), 113.66 (4 x CH aromatic), 114.07 (2 x CH aromatic), 121.51 (2 x CH aromatic), 125.42 (CH aromatic), 127.17 (2 x CH aromatic), 129.11 (4 x CH aromatic), 129.23 (4 x CH aromatic), 130.09 (2 x CH aromatic), 136.28 (2 x CH aromatic), 139.83 (2 x C aromatic), 145.03 (2 x NHC aromatic), 145.12 (2 x NHC aromatic), 172,56 (2 x C=O). ESI(+)-MS $CH_3CN$ [C = 0.5, SC = 30, EC = 3] *m/z* (rel. int.): 609 (100, M + $H^+$), 462 (50, M-CONHCHBn + $H^+$), 315 (100), 120 (70). HRMS $ES^+$ for $C_{38}H_{37}N_6O_2$ *m/z*: $[M+H]^+$ Calc. 609.2978, found: 609.2975.

**2,2′-(1,4-Phenylene)bis-[5-(2-methylthioethyl)-3-(phenylamino)imidazolidin-4-one]** (**5o**). Orange solid, mp 125-127 °C. $R_f$ 0.45 (EtOAc/c-$C_6H_{12}$ 1:1). IR (neat), $\nu_{max}$ ($cm^{-1}$): 3284, 2916, 1695, 1601, 1445, 1409, 1091. $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ 2.00 (2H, s, NH), 2.00-2.04 (4H, m, $CH_2$), 2.30 (6H, s, $CH_3$), 2.62-2.64 (4H, m, $CH_2$), 3.74-3.77 (2H, m, CH)), 4.03 (2H, s, CH), 5.92 (2H, s, NHPh), 6.92 (2H, t, $^3J_{HH}$ 7.9 Hz), 7.12 (4H, d, $^3J_{HH}$ 8.7 Hz), 7.24-7.27 (4H, m, CH aromatic), 7.40 (4H, dd, $^3J_{HH}$ 8.7, $^3J_{HH}$ 7.9 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ 15.40 (2 x $SCH_3$), 30.50 ($CH_2$), 30.53 ($CH_2$), 34.10 (2 x $CH_2$), 34.14 (2 x $CH_2$), 68.00 (2 x CH), 68.03 (2 x CH), 75.80 (2 x CH), 75.83 (2 x CH), 113.22 (2 x CH aromatic), 123.11 (2 x CH aromatic), 126.00 (CH aromatic), 130.40 (CH aromatic), 136.50 (2 x C aromatic), 153.31 (2 x NHC aromatic), 173.20 (2 x C=O), 173.22 (2 x C=O). ESI(+)-MS $CH_3CN$ [C = 0.5, SC = 30, EC = 3] *m/z* (rel. int.): 577 (100, M + $H^+$), 486 (10), 446 (5, M-$COCH(CH_2)_2SMeNH$ + $H^+$), 355 (10). HRMS $ES^+$ for $C_{30}H_{37}N_6O_2S_2$ *m/z*: $[M+H]^+$ Calc. 577.2419, found: 577.2418.

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## Supplementary Material

Stereochemistry analysis, examples of $^1$H and $^{13}$C NMR spectra are available as supporting information.

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